STUDIES OF HUMAN PHYSIOLOGY AT 17,500 FEET IN MOUNTAIN ENVIRONMENT

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ABSTRACT

Shifts in body water and electrolytes, and changes in serum proteins and certain hormones, which occur in response to hypoxia will be studied during the fifth year of work in an all-weather laboratory situated at 17,500 feet on Mount Logan, Canada. Special emphasis has been and will be given to studies of the retinal circulation which we believe mirrors changes in less accessible micro-circulations elsewhere in the body. The changes in water, electrolytes, proteins and hormones are believed to be major influences on the symptom complex called acute mountain sickness which we postulate may occur in persons hypoxic at sea level from a variety of diseases and injuries. Our major objective is to elucidate the relationship of these changes one to another, to the retinal pathology previously reported from our earlier work at this facility, and to hypoxic conditions studied at lower altitudes and at sea level.

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Objectives

The proposed research is designed to study the effects of acute hypoxia principally upon the movements of body water and electrolytes; the modification of these shifts by therapeutic and prophylactic medications such as acetazolamide and steroids; the impact of these changes upon the microcirculation as evidenced by changes observed in the retinal circulation; and the relationships of these changes to acute mountain sickness (AMS): a syndrome which we believe may occur in many hypoxic individuals, including patients at sea level.

The procedures are designed to test the hypothesis that acute hypoxia initiates, though it may not necessarily cause, a series of integrated changes in the body, amongst them movements of water and electrolytes with changes in the micro-circulation, and that a number of hormones are involved in these changes, either primarily or secondarily.

Background

General: The adverse effects of high altitude have been known for more than 500 years but, until the 19th century, poorly understood. Paul Bert's (1877) monumental work "Barometric Pressure", contains an excellent review of the history of altitude studies. At the turn of the century, Barcroft, Mosso, Haldane, Longstaff, Loewi, Zuntz, and others published many of the basic observations on which our present knowledge rests. The beginnings of aerial warfare in World War I stimulated studies of the effects of rapid ascent which were continued in the Canadian Rockies, the South American Andes, the Alps, and the Himalayas, from 1920 onward by Douglas, Henderson, Bock, Edwards, Dill, and many others. Van Liere (1942) collected the significant studies made to that time, and vonMuralt (1962) has briefly summarized the history of high altitude studies up to 1962. Fenn, Otis, and Rahn, Luft, Dill, and particularly Hurtado and Monge for many years have studied the broad aspects of hypoxia in man, and the mechanisms of acclimatization

During World War II the rapid development of high altitude aircraft necessitated urgent studies of hypoxia, and air combat created involuntary and tragic human experiments at altitudes above 20,000 feet from which death or permanent disability often resulted. The cruel reality of high altitude mountain warfare was harshly demonstrated in 1962 when the acclimatized Chinese armies easily overran Indian troops hastily brought up to the Himalayan frontier from low altitude (Singh, 1969). Currently the ease and speed

with which skiers and mountaineers are transported from normal to high altitude has produced further in vivo experiments, from which have developed quite unexpected observations such as high altitude pulmonary edema, and - in our recent studies - retinal pathology due to altitude.

The effects of oxygen lack can be studied in several ways. A low pressure chamber can be evacuated to the desired atmospheric pressure and experimental subjects or animals kept in a controlled environment while studies are made. Most of the work done during World War II and immediately thereafter was conducted in hypobaric chambers, and was for the most part directed at observation of acute effects following acute exposure. The principal investigator for the Logan High Altitude Project directed a long-term study of acclimatization in a chamber (Houston, 1947) where many parameters were studied during a 35 day ascent from sea level to a simulated altitude of 29,000 feet.

The hypobaric chamber, generally located in a sophisticated laboratory in close proximity to all of the benefits of a modern hospital makes it possible to isolate the effects of oxygen lack from the other influences which occur in the mountains. It is a test tube environment. Psychologically it is also an unreal environment, and long-term studies conducted in the low pressure chamber confront problems such as boredom, confinement, claustrophobia, physical inactivity, and introspection, in addition to the direct impact of hypoxia.

Observations conducted in the mountains are also affected by other obstacles: the effects of cosmic rays and ultra-violet radiation from sunlight unfiltered by the earth's atmosphere; cold, wind, low humidity, and the constraints imposed by heavy clothing, inadequate shelter, limited fluids and food, and the usual necessity of strenuous work, all introduce variables into any study made during the course of a mountain expedition. Newcomers to the mountain world are also influenced by the isolation, and the fearful heights and depths.

Nevertheless mountain laboratories which can provide sea level living conditions have been used for almost a hundred years to study the effects of altitude. On Monte Rosa, Mount Evans and Pikes Peak, and at Cerro de Pasco, and elsewhere permanent laboratories enable detailed study of altitude in both acute and chronic exposure up to 16,000 feet. Pugh (1962) reported studies made at 19,000 feet over a period of several months in the Himalayas. A large amount of material has been collected on Aconcagua during excercises in which several hundred military troops ascended to 20,000 feet (Albrecht, 1969).

Although few mountaineering expeditions can provide facilities suitable for careful studies, there are a number of well-equipped laboratories on high mountains:

TABLE 1 - HIGH ALTITUDE RESEARCH STATIONS

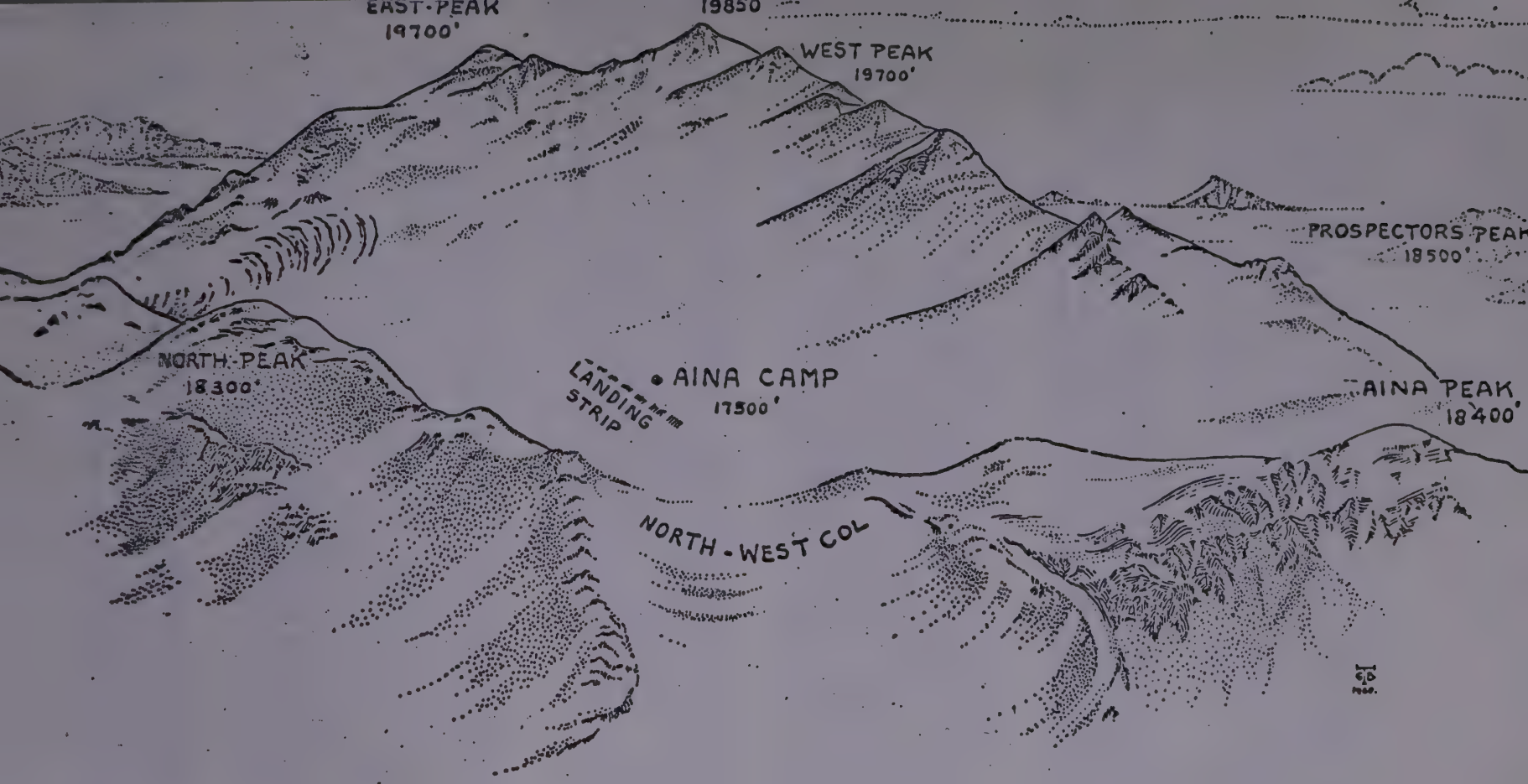
Logan High, Canada	5300 m - 17,500 feet
Ticlio, Peru	4880 m - 16,000 feet
Morococha, Peru	4530 m - 14,900 feet
White Mountain, Summit Laboratory, Calif.	4340 m - 14,250 feet
Mount Evans, Colorado	4300 m - 14,100 feet
Cerro de Pasco, Peru	4200 m - 13,770 feet
Mina Aguilar, Argentine	3990 m - 13,100 feet
White Mountain, Barcroft Laboratory, Calif.	3800 m - 12,470 feet
Jungfraujoch, Switzerland	3454 m - 11,333 feet

Logan High, several thousand feet higher than these, comes close to the stable environment required for good work. The laboratory (described in more detail under Facilities Available) provides electricity, adequate, comfortable working and living space kept at room temperature, a kitchen which can provide either the customary sea level menu or special diets, protection from the extremes of sunlight, temperature, and psychologic hazard, beautiful surroundings, with ample room for exercise.

Two other methods of studying hypoxia in man should be mentioned. Actual flights in aircraft or balloons first conducted over a century ago, (Bert, 1877) provide rapid, easy access to the higher atmosphere. Their limitations are obvious and need not be reviewed. The second method - providing an atmosphere which is normal in pressure but low in oxygen - provides easy evaluation of hypoxia under laboratory conditions at sea level. Although the constraints imposed in a low pressure chamber are minimized by such low oxygen gas mixtures, other constraints make it difficult to conduct experiments for more than a few hours using this technique.

We have carefully considered whether the proposed work might be better done in a hypobaric chamber at sea level. The high mountains introduce other variables beside hypoxia: cold, wind, isolation, exposure to cosmic and actinic radiation, all of which complicate and confuse the effects of oxygen lack. These influences make observations done in the course of climbing expeditions less valuable than those in a hypobaric chamber. Unless such variables can be brought within "normal" range, the hypobaric chamber is a better laboratory than the mountains.

We feel that Logan High does offer a near "normal" environment because the shelters are comfortable and warm; exposure to wind, cold, and excess sun can be minimized or completely avoided. Good food, adequate fluids and a relaxed, friendly group make Logan High much like home. There is ample space for walking or other outdoor activities (frisbie is popular). Boredom is non-existent. By contrast the hypobaric chamber is cramped,



MOUNT LOGAN

St. Elias Mountains

and even the large modern chambers limit activities, producing a distinctly experimental atmosphere which is hard to dispel. Boredom comes soon; exercise is limited to cycling in place or calisthenics; companionship is distinctly limited. The chamber may provide an environment which is "normal" in all respects except for oxygen pressure, but it is not an environment conducive to "normal living".

Perhaps the greatest advantage which Logan High offers over the hypobaric chamber is our ability to study acclimatized subjects (the support team) concurrently with the acutely exposed volunteers and the partly acclimatized scientists. For the same effort we are able to get observations on several different groups.

Logan High Project: For the past fifteen years the Arctic Institute of North America has sponsored a number of studies of the biological and physical sciences in a large unspoiled area of the Canadian Yukon. The Institute has maintained a facility on the Alaska Highway at an altitude of 2,600 feet which contains workshop, laboratory, library, and living conditions to accommodate 50 or 60 persons. Several hundred individuals have pursued research leading to advanced degrees, and many post-doctoral papers have been published, (Arctic Institute, 1970).

In 1966, the Institute decided to add studies of high altitude to this comprehensive environmental program. Mount Logan, highest summit in the Yukon (19,100 feet) is 75 air miles from the Kluane Lake facility. Described as the largest isolated mountain mass in the world, Logan has a summit plateau approximately ten miles long and two to four miles wide, consisting of smooth, gently sloping snow fields, surrounded by peaks which provide partial shelter from extreme winds, (See attached sketch).

During the summer of 1967 a prefabricated wooden building was erected at 17,500 feet by a party of mountaineers who achieved acclimatization during a slow climb to the laboratory from an aircraft landing lower on the mountain. In 1968, the laboratory was reoccupied and scientists demonstrated the feasibility of accurate, sophisticated work in this environment. The long frigid sub-arctic winter darkness makes that season impractical for work on Mount Logan; weather tends to be fickle and unpredictable during the spring and fall, so that June, July and August are optimal working months, during which time there is almost continuous daylight, generally favorable weather and few periods of more than one or two days of storm.

Logan High was again occupied from early June to early August in 1969 and 1970; new buildings were required because of the settling, deep beneath the cumulative snow cover, of the first wooden building, and these are described below. Six or eight climbers comprise the support party each year, and ten

Canadian Forces have served as subjects for the four to six scientists. A Canadian military STOL aircraft has been available to transport personnel and equipment to Kluane Base and has made successful parachute drops of supplies at Logan High. Thus the logistics are by now well tested and generally suitable. Details are given in Procedural Methods.

Observations made during the four seasons in which Logan High has been occupied have led us into certain areas in which we have found it essential to extend the work of others conducted at lower altitude. It is important to note that each increment of altitude above 13,000-14,000 feet causes an increment of physiologic change which is greater than the increment caused by a similar increment of altitude at lower elevation. The higher one goes, the more difficult becomes each adaptation.

Specific: In striking contrast (Dill, 1968) with the people who reside at high altitude (and even with patients with cyanotic congenital heart disease) (Davies & Gazetopoulos, 1965), people suddenly exposed to marked arterial hypoxemia* become ill. This illness is seen in its most clearly delineated form in acute mountain sickness (AMS). This is a debilitating and "rarely" fatal disease described by many mountaineers (for example, Whymper, 1872; Howard-Bury, 1921; Leigh-Mallory, 1925; Tilman, 1938) and by numerous investigators (Monge, 1937; Carson, 1969; Singh, 1969). It affects people abruptly elevated to altitudes above 10,000-12,000 feet.

The syndrome of AMS is characterized by breathlessness, headache, restlessness, disturbed sleep, Cheyne-Stokes respiration, anorexia, nausea, and vomiting. Rare deaths from pulmonary edema or cerebral edema (Hultgren, et. al., 1962; Singh, et. al., 1969) have been described. These symptoms and signs are non-specific and may all be seen at sea level in patients with arterial hypoxemia from many causes.

Singh, et. al., (1969), Shields, et. al., (1969) and others have noted that the onset of AMS is usually delayed for several hours after ascent and that the symptoms are at their worst 24 to 48 hours after arrival at altitude. Gradually the symptoms and signs regress and recovery is marked by the appearance of a series of integrated changes (respiratory, renal, vascular, hematological, biochemical, etc.) which taken together constitute acclimatization (Houston, 1947). A few individuals, the proportion being higher at higher altitudes, go on to develop the syndrome of chronic mountain sickness: a condition in which it appears that some of the adaptations to hypoxia may have themselves become harmful (Monge, 1943).

Because of this characteristic delay, Singh, et. al., (1969), Houston (1951), and some others, feel that hypoxia itself may not be the direct cause of the

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*Hypoxia by common usage is replacing the less precise term anoxia, and means ambient air of lowered oxygen content. Hypoxemia, a more restrictive term, means diminished oxygen content and pressure of (arterial) blood, which may be due to a variety of causes, including altitude or low oxygen atmosphere.

illness, and postulate that hypoxia triggers a sequence of vascular and hormonal events which finally result in the syndrome of AMS. Recent therapy used in AMS (Singh, et. al., 1969; Landowne, et. al., 1969; Gray, in press; Severinghaus, 1965) has been more effective than cytochrome, gland extracts, ammonium chloride, methylene blue, etc., in vogue years ago.

Patients with arterial hypoxia due to cyanotic congenital heart disease (Rennie, 1969) and natives dwelling permanently at high altitudes (Rennie, in preparation) have excessive proteinuria, the pattern being characteristic of glomerular disease (Joachim, 1964). We have shown (Rennie, 1970) in mountain climbers during acclimatization to high altitudes, that the urine protein concentration of early morning specimens of urine, adjusted for osmolality to compensate for changes in diuresis, correlates with the altitude at which the urine samples were taken, and the correlation is even higher when the urine protein at the altitudes experienced 24 and 48 hours before sampling are taken into account. In other words, urine protein concentration clearly reflects changes in altitude after a delay of 24 to 48 hours. This delay, and the fact that it is the same as the delay in the onset of AMS, might suggest that both may be caused by the same factors.

Following sudden hypoxia, two main changes occur in the blood: a sudden hemoconcentration (Abderhalden, 1896; Campbell and Hoagland, 1901; Gregg, et. al., 1919) due to a reduction in plasma volume (Grawitz, 1895; Dreyer and Walker, 1920; Hannon and Shields, 1968) and a slower increase in circulating red cell mass (Hurtado, et. al., 1945; Merino, 1960; Reynafarje, 1957; Mylrea and Abbrecht, 1970). Hannon, et. al. (1969) demonstrated a rapid shift of water into the intracellular space at the expense of the extracellular compartment, including the plasma. This flow is maximal over the first three days at altitude, and is probably the major cause of the hemoconcentration. They also found a brisk fall, on acute exposure to high altitude, in extracellular cations (the product of extracellular volume and the summated serum concentrations of Na, K, Mg, and Ca). They point out that the fate of these cations is as yet unknown, saying: "the cation and anion levels in these two compartments, particularly the intracellular, obviously need further investigation".

We noticed suggestions of clinical hypovolemia (thirst, dry tongue, rapid pulse, falling blood pressure, oliguria) as well as symptoms suggesting cerebral edema (papilledema, headache, disorientation) in some unacclimatized subjects taken rapidly to 17,500 feet in 1968 and 1969, (Gray, et. al., in press). We therefore felt it desirable to investigate fluid shifts more fully in 1970. In climbers studied in the Himalayas Rennie (1970) had found variable changes in the concentrations of different serum proteins measured immunologically, chemically and by electrophoresis. The validity of these observations was confirmed in a pilot study on Mount Logan (17,500 feet) in 1969 (Rennie, in

preparation). Briefly, the concentration of total serum protein rises on acute exposure to high altitude, confirming the observation by Hurtado, et. al. (1945) that total serum protein, on acute exposure to various altitudes rises much more rapidly than does the hematocrit. The rise is partly a reflection of hemoconcentration due to movement of fluid out of the vascular space (Hannon, et. al., 1969), but this does not explain why protein concentration rises more than does the hematocrit, nor why the different proteins should behave variably.

In experiments on Mount Logan in 1970 we found (in fit male subjects pre-treated with acetazolamide):

1. an increase in Evans Blue space (in 7 out of 8 subjects);
2. a decrease in total body water (in 5 out of 6 subjects); and
3. an increase in extracellular fluid (in 4 out of 5 subjects).

These results are at variance with those of Hannon, et. al., and make the results of the serum protein studies (see below), for example, difficult to interpret.

As a logical extension of the studies of Hannon and Shields (1969), we assumed that in any condition producing hypoxemia, water and sodium would move into red cells, which would therefore enlarge. Having developed a suitably accurate and reproducible technique for measurement of intracellular sodium and potassium levels (see below) in 1969 Rennie made a pilot study of mice subjected to a simulated altitude of 18,000 feet in a hypobaric chamber; this showed a significant increase in red cell sodium concentration which was maximal after 24 hours of exposure.

Thus after 24 hours exposure to 18,000 feet (hypobaric chamber) the mean intracellular sodium was 3.7 mEq/L in the control mice and 11.3 mEq/L in the "hypoxic" group of mice. These studies were made on Logan in 1970: in the male subjects acutely exposed to 17,500 feet, mean intracellular sodium was 3.5 mEq/L at Kluane and 11.5 mEq/L on Logan. (Rennie, et. al., in preparation).

While these experiments were being done, Mylrea and Abbrecht (1970) showed that red cell volume in mice in hypobaric chambers increased markedly in proportion to the degree of hypoxia. These authors postulated the mobilization of new large cells into the circulation without considering that fluid shifts might be the cause.

In the experiments on Mount Logan (17,500 feet) the concentration of serum proteins tended to rise abruptly on exposure to high altitude, and then to fall gradually while subjects remained. After rapid descent to Base Camp at Kluane Lake (2,600 feet) there was a much greater fall, sometimes to levels well

below the initial Kluane Base values. Fluid shifts out of and into the extravascular space cannot be the only cause of the protein concentration changes observed, however, because these vary widely from one protein to another. Thus ascent to high altitude is accompanied by a 13% rise in albumin, a 27% rise in IgG and only a 7% rise in IgM as measured by immuno-diffusion. Moreover, the final Kluane "sea-level" values, as a percentage of the initial Kluane values, were 94% for albumin, 101% for IgG and only 79% for transferrin.

Singh, et. al. (1969) proposed an elaborate scheme of reactions and secondary adjustments to abrupt high altitude exposure, some of which were investigated by Slater, et. al. (1969), who showed that with exposure to altitude, rates of aldosterone fell despite an increase in plasma renin activity and in cortisol secretion. Slater attributed the reduction in potassium excretion rates to the lowered aldosterone levels and to the extracellular alkalosis which occurs at altitude. He was unable to explain the changes in aldosterone secretion in terms of known control mechanisms, and did not measure body fluid compartments or intracellular electrolytes.

In summary: we conclude from our own work, and that of others, that sudden hypoxia is accompanied by an abnormal permeability of blood vessels to proteins and an abnormal flow of water and electrolytes into cells, and that these changes are important features of the syndrome of acute mountain sickness, which may occur in any hypoxemic person. There is, however, apparently conflicting evidence on the body fluid compartment studies, some of which are hard to reconcile with the changes found in aldosterone secretion.

During our early work on Mount Logan (1968) we observed several instances of retinal hemorrhage in individuals both acutely and gradually taken to altitude, which could not be attributed to the usual causes. McKeown (1941) and Baum and Bulpitt (1970) have reported that between 15% and 42% of all newborns show retinal hemorrhage regardless of the duration or difficulty of labor or of notable hypoxia during delivery. Eastman (1954) describes the fetus as living in atmosphere equivalent to 32,000 feet and speculates on the mechanism by which the fetus "acclimatizes" to "Mount Everest in Utero". We have been unable to find published accounts of retinal hemorrhage in healthy individuals acutely or chronically exposed to high altitude except for a brief mention by Singh (1969) but personal experience (Schumacher, 1969; Houston, 1953) suggests that such events may not be uncommon. Retinal hemorrhages are not infrequently seen (when looked for) in patients with conditions causing severe acute hypoxia (Baker); often some accompanying condition other than hypoxia is used to explain these.

Our observations and literature search in 1968 led to a more careful set of studies in 1969 and in 1970 (Frayser, 1970; Frayser in press, 1970). These included retinal photographs taken before and after rapid ascent to 17,500 feet

by the volunteer subjects and after gradual ascent by the support party who were at least partly acclimatized when studied. Retinal circulation time was measured in several individuals using fluorescein (Hickam and Frayser, 1965); retinal arterial and venous oxyhemoglobin saturation were estimated (Hickam, 1963) and changes in dimension of retinal vessels measured directly from the photographs. In the 1969 studies (Frayser, 1970) retinal hemorrhages were found in three of the eight acclimatized support party members, and in six of the 17 individuals (scientists and volunteer subjects) taken rapidly to 17,500 feet; no significant relationship was found between the incidence of hemorrhage, the severity of AMS or of headache. Pre-medication with acetazolamide appeared to decrease the incidence of hemorrhage somewhat. Only one of the hemorrhages was symptomatic and the remainder would have been undetected had they not been sought. In 1970 hemorrhages were noted in one of the eight members of the acclimatized support team, and in two of 14 persons acutely exposed, (Frayser, in preparation). Measurements of photographs taken in 1969 and 1970 indicate that all subjects pre-medicated with acetazolamide show less increase in tortuosity (Frayser, in preparation). Individuals who showed hemorrhage in 1969 and 1970 were examined several weeks after return from Logan High; all showed disappearance of the hemorrhage without scarring, except that the macular hemorrhage (the only one to cause symptoms) showed a small residual visual scar and defect. From these observations we postulate that retinal hemorrhage is not uncommon at high altitude, but is usually not sought because it is asymptomatic. By extension we speculate that retinal hemorrhage may be more common than realized in many conditions which cause acute - or chronic - hypoxia.

We have prepared several hypotheses in an effort to understand retinal hemorrhage; they are as follows:

1. Hypoxia may produce changes in the normal relationships between retinal blood flow, vascular volume and intraocular pressure which allow pressure surges (systolic ejection, exertion, straining) to be transmitted less damped to dilated, hypoxic and hypocapnic vessels, thus leading to rupture.

2. Hypoxia may produce localized endothelial damage in the arterial system which may allow the vessel walls to become permeable to protein and other substances normally confined within the vessel.

3. Changes in acid base balance together with low pO_2 may alter the metabolism and integrity of cells forming the vessel walls, permitting seepage of blood.

4. The vascular integrity may be altered by shifts in intracellular water and electrolytes resulting from shifts in renin, angiotensin and/or aldosterone levels.

These hypotheses will be tested by measurements of intraocular tension at rest and during or after exertion, together with fundal photographs, determination of fluorescein circulation time, measurement of retinal HbO_2 Saturation, and by examination of the relationship of hemorrhage to the values found in the water, electrolyte, and renin-aldosterone-ADH studies. The studies of body fluid and electrolyte shifts proposed are directly related to studies made in 1970 and proposed for subsequent years relevant to the regulation of respiration and of cerebral blood flow.

Another hypothesis which we propose to examine is that changes in the retinal circulation mirror changes in other areas (such as the brain) which cannot be readily observed but must be studied indirectly. Investigators over the past ten years have established that pulmonary ventilation is a function of CSF (H^+) in some area within the medulla (Severinghaus, 1963; Pappenheimer, 1965; Miller, 1966; and Mitchell, 1965). CSF (H^+) is actively regulated by transport of ions across the blood-brain barrier (Kellogg, 1965; Bradley, 1967; Severinghaus, 1963), probably at the capillary-glial interface. Severinghaus has studied these changes in man at altitude, but further observations are needed. It has also been suggested (Skinhoj, 1966; Severinghaus, 1967; Fencl, 1969) that cerebral blood flow is directly influenced by CSF (H^+) (Hornbein, 1966) but here too a great deal of work remains to be done to relate CSF (H^+) to ventilation and to changes in cerebral blood flow. Though many of the necessary observations can be made only in animals, or in man under meticulous laboratory/hospital conditions (low pressure chamber studies); others can be conducted in a mountain laboratory such as Logan High.

Venous compliance is one circulatory measurement which can be readily made in a mountain laboratory (Weil, 1969; Gray, in press), and may be directly related to the changes postulated above.

Rationale

The proposed studies are based on the belief that acclimatization to hypoxia consists of a series of integrated changes in virtually all systems of the body, which tend to restore the oxygen tension within the cells to that normally present at sea level. Movement of water and electrolytes, changes in protein concentration and character, and alterations in hormal secretion are both cause and result of these integrations, and the elucidation of their interaction provides the major rationale for this work. We use the retinal circulation as a micro-circulation in which the effects of hypoxia can be easily observed in an effort to correlate the above changes in this circulation, and, by extension other circulations as well. An additional indicator of tissue hypoxia may be the urinary lysozyme excretion rate, dependent on function of the proximal tubules which are known to be high oxygen users.

Movement of water and electrolytes into red cells will increase their size, water and sodium content and their volume; this should be followed by an increase in plasma renin levels, angiotensin and aldosterone levels and an increase in anti-diuretic hormone in response to hypovolemia and increased plasma osmolality. It is these changes and their sequence which we expect to demonstrate.

Procedural Methods

Three categories of experimental subjects are available to us for study:

1. Ten military troops volunteering from the Canadian Forces; *
2. Eight mountaineers, engaged as support party; and
3. Five scientists participating in the work.

Constraints of time and geography, and considerations of safety will require that each category be handled somewhat differently. All categories will be thoroughly screened to ensure fitness.

Category 1 (troops) will be fully briefed about the project before being accepted. If possible some will serve as subjects in low pressure chamber runs to be done in Toronto early in 1971. Soon after arrival at Kluane Lake Base Camp, all ten will be fully studied (control observations). They will be placed on Canadian C rations and careful intake/output measurement on arrival, and will continue on this diet until the experiment ends. Five of these troops will then be given acetazolamide, and certain tests repeated 24 hours later; this group will be flown to Logan High after 48 hours of pre-medication. The second five, without pre-medication, will be flown to an intermediate camp at 9,600 feet, where at least some of the studies done at Logan High will be made. After five days the group at Logan High will be taken to Kluane Base, and the group at the intermediate camp taken to Logan High, remaining for five days before descent to Kluane Base.

Category 2 (support group). These individuals will arrive at Kluane Base in early June (too early for Base studies), be flown to a glacier landing at 10,000 feet, and will then take ten days to climb Logan; experience shows that enough acclimatization is thereby achieved to permit work at altitude with minimal symptoms. This group will thus have been at Logan High for several weeks before the scientists arrive and are able to study them. They represent an acclimatized category. Unfortunately they will not be brought down to Kluane Base until the scientific group has left, so no control studies will be possible, unless we are able to use some of this category as subjects in the low pressure chamber runs which we hope to accomplish in the early part of 1971.

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* one troop = one individual

Category 3 (scientists). All of the individuals who do the studies are anxious o be subjects insofar as this will not jeopardize their function. All will probably scent to Logan High directly from Kluane Base after 48 hours pre-medication ith acetazolamide; they will be studied before ascent, both before and after cetazolamide, at Logan High, and - if possible - after descent.

Thus we will study about 20 individuals: some acutely exposed after pre-medi- ation, some sub-acutely exposed without medication, others chronically exposed fter acclimatization. By careful scheduling of the procedures we expect to obtain scatter of data to cover a wide range of time and people without subjecting any dividual to excessive blood-letting, manipulation, or risk. The ten volunteer oops are our most important subjects and will be given priority attention.

In each case, then, in summary:

a. the volunteers will receive full explanation in advance;
b. the volunteers will be on a fixed diet of Canadian C rations;
c. daily weight, fluid and food intake and urine output will be measured;
d. daily clinical observations will be made by the physician in charge;
e. arterial blood will be taken for PaO_2, $PaCO_2$ and pH measurements (I. L. electrode and meter); and
f. venous blood will be taken without compression and, unless otherwise dictated, before rising in the morning.

At least one complete study will be made on each subject at each altitude. The d cell size and electrolyte studies and the urine lysozyme studies will also be peated on return to low altitude.

i. Red cell size. Hemoglobin (cyanmethemoglobin method: Dacie & Lewis, 1963), hematocrit (microhematocrit method) and red cell volume (Coulter Counter) will be measured (in duplicate, in Chicago) using specimens drawn into appropriate Unopette containers.

ii. Red cell water and electrolytes. Sodium, potassium and chloride will be measured on 20 lambda samples taken into lithium chloride Unopettes, from whole blood and from the plasma column of the microhematocrit tube straight after immediate centrifuging. Measurement (in Chicago) will be by flame photometer (International Laboratories). The intracellular electrolyte concentration is calculated from the plasma and whole blood concentrations and the hematrocrit, corrected for trapped plasma.

The measurements of intra-red cell electrolytes will be repeated using the methods of Funder, et. al., (1966) by which red cell water can also be measured, after evaporation of the red cell column to dryness.

ii. Body fluid compartments. These will be measured in resting, fasting subjects, using the methods of Hannon, et. al., (1969). Thus for plasma volume: Evans Blue; for total body water: 4-aminoantipyrine; and for extracellular water: sodium thiocyanate will be used, the concentrations in venous blood being determined immediately (at the Kluane Base laboratory).

iv. The renin-antiotensin-aldosterone-ADH system. The subjects will be on a constant diet. The following will be measured:

a. weight
b. repeated 12 hour urine volume, sodium, potassium and chloride, creatinine, urea, (Auto Analyzer, using standard manifolds) and aldosterone (Mayes, 1970)
c. in venous blood, taken before rising (and, if possible, after two hours ambulation), plasma osmolality (Advanced Instruments Osmometer); renin (method of Haber, 1970), aldosterone (method of Mayes, 1970); ADH (method of Yoshida, 1963), cortisol; all will be measured in Indianapolis and Chicago.

v. Urine lysozyme in aliquots of timed urine specimens will be measured by the method of Osserman & Lawlow (1966), which depends on the lysis of a suspension of Micrococcus lysodeikticus in agar. The measurement will be made on fresh specimens of urine, at Kluane.

Expected Data; We expect to find an increase in red cell size, water, and electrolyte content, with evidence of movement of fluid into cells. We may, however, again find, on the compartment studies, evidence of increased extra cellular fluid and decreased total body water. Because of the work of Slater, et. al. (1969), we expect to find a decreased aldosterone secretion, but the control of aldosterone at high altitude seems to be obscure and these levels, and the fluid changes, may be very variable in different people, at different altitudes with different fluid intakes. We would expect increased ADH secretion. We expect hypoxia, if present, to increase lysozymuria.

We expect to find a direct relationship between the magnitude of the electrolyte and water shifts, the changes in hormone assay, and the incidence of retinal hemorrhage and changes of intraocular pressure. These may be correlated with changes in vascular permeability (retinal fluorescein studies, urinary protein excretion). Though careful clinical examinations will be made regularly we do not expect to find much correlation between such observations and other data.

The correlation of red cell size, red cell electrolyte content, water compartment studies and studies of the renin-aldosterone and ADH systems should show whether there is really a shift of fluids on exposure to hypoxia, and, if there is, whether any hormonal changes precede or follow it, and therefore whether they may be causative.

Significance of the Proposed Work

The studies undertaken on Mount Logan during the past four years and those proposed for the future have the following importance.

1. Laboratory work at Logan High (17,500 feet) is feasible and will uncover changes in human physiology which do not occur or are small at lower altitudes. Thus we can add important data to that gathered elsewhere by others.

2. Hypoxia causes shifts in body water and electrolytes, and related responses in hormones; all of which may be major determinants in the symptom complex known as acute mountain sickness - a syndrome which may occur in hypoxemia from many causes.

3. Signs and symptoms seen in many diseases or injuries which cause hypoxemia may be due more to the above mentioned fluid and electrolyte shifts and hormonal changes than to oxygen lack per se.

4. The vascular changes which we have observed and reported in the retinal circulation may be characteristic of changes occurring in less easily observed micro-circulations elsewhere in the body.

Our thesis is that changes which occur in normal individuals in the abnormal atmosphere of 17,500 feet are more striking than those seen at lower altitude, and more "physiologic" than those seen in long hypobaric chamber runs, and will cast light on the responses of diseased persons in sea level atmosphere.

Facilities Available

Logan High consists of a cluster of double-walled nylon shelters with wooden floors, space heaters, propane generator, and ample supplies of food, drugs, oxygen and fuel. This laboratory complex is located on the upper portion of a large snow plateau at an altitude of 17,500 feet beneath the several summits of Mount Logan, Canadian Yukon.

Logan High is serviced by air through a Helio Courier fixed-wing aircraft which has a service ceiling of 22,000 feet and a payload of over 500 pounds. This aircraft lands on skis at the laboratory and on retractable wheels at the Kluane base facility.

We have also demonstrated the feasibility of using helicopter support (Jet Ranger, with ceiling close to 20,000 feet and payload of more than 300 pounds) as back-up for our aircraft. Several Jet Rangers are on call at all times during the project.

Logan High is about 75 air miles from Kluane Base facility (2,600 feet) and the weather is quite different at the two locations. Radio communications are maintained around the clock and weather observations reported every four hours routinely, and more often if needed. With the cooperation of the Department of Transport, Whitehorse, Yukon, we are able to gage weather adequately for our purposes.

Flight records over the past four summers show that during the 124 July days when the project has been in operation, we have made 97 landings and takeoffs at Logan High on 52 flying days and have been unable to fly because of weather on 39 days. Rarely have we been prevented from landing at Logan High for more than two consecutive days because of bad weather.

An intermediate camp (Divide, 9,600 feet) has been used as a staging camp as it will be in 1971. This camp, about halfway from Kluane Base to Logan High, has been maintained for meteorologic and glaciologic work for the past eight years.

Kluane Base facility is located at Mile 1054 on the Alaska Highway on the shore of Kluane Lake, which is the largest lake in the Yukon. The facility consists of a number of permanent wooden buildings which provide housing, workshops and laboratories, and eating and recreational space for the more than 50 persons who have been studying many biological and physical sciences in this region for 15 summers. These investigators make up the Icefield Ranges Research Project, sponsored by the Arctic Institute of North America and the American Geographical Society, and directed toward a long-range comprehensive environmental study of this large unspoiled wilderness area. The high altitude studies were added to the Project in 1967, but additional support is needed as the high altitude work has expanded and demonstrated its feasibility and promise.

In 1970 a large log cabin near Kluane Base was remodeled to serve as a physiology laboratory. It is provided with heat, water and electricity and, like the main Base, has telephone connection to the outside. Thus far we have kept only expendable supplies at this laboratory. The investigators have been able to bring the equipment needed for the component studies, due to the cooperation of their institutions. We are particularly appreciative of the cooperation of the Institute of Environmental Medicine, Toronto, through which the Canadian Armed Forces have given much help.

A 2,000 foot gravel airstrip runs through Kluane Base facility and can accommodate various aircraft, the largest being a Canadian Forces STOL Buffalo, which can carry a payload well over 10,000 pounds and has made many parachute drops for us at Logan High.

Finances

The annual cost of the Project is approximately $140,000 per year. This cost includes stipends to the Scientific Coordinator, salaries for technical staff members and logistic support personnel, transportation to and from the field, subsistence, aircraft services, radio communications, shelter, etc. In addition, the Canadian Forces supply a ten-man test team complete with transportation, field equipment and field supplies. Individual investigators are responsible for obtaining their own funds for support of their participation.

The budget breakdown follows:

Salaries, stipends and payroll costs	$	30,000
Travel to and from field station		8,000
Field subsistence and housing		13,000
Support equipment and supplies		30,000
Communications and shipping		10,000
Pre-project planning and mobilization		4,000
Post-project, conferences and reporting		5,000
Subtotal	$	100,000
Administrative expense (at 40%)		40,000
Total	$	140,000

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